*Short Note*

# Ethyl 7-Acetyl-8a-methyl-3-(1-phenyl-1*H*-tetrazol-5-yl)-1,4,4a,5,6,8a-hexahydro-7*H*-pyrano[2,3-*c*]pyridazine-1-carboxylate

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**Abstract:** The Diels–Alder reaction of ethyl 3-(1-phenyl-1*H*-tetrazol-5-yl-1,2-diaza-1,3-butadiene-1-carboxylate with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (methyl vinyl ketone dimer) regioselectively afforded the corresponding 3-(tetrazol-5-yl)-hexahydro-7*H*-pyrano[2,3-*c*]pyridazine in quantitative yield. An X-ray crystal structure of this cycloadduct is reported.

**Keywords:** tetrazoles; diaza-1,3-butadiene; pyrano[2,3-*c*]pyridazine; methyl vinyl ketone dimer; diels-alder reactions; X-ray structure

## 1. Introduction

Conjugated nitrosoalkenes and azoalkenes are effective and versatile building blocks for the construction and functionalization of heterocyclic systems, acting mainly as electron-deficient heterodienes in hetero-Diels–Alder reactions or as Michael-type acceptors in conjugate 1,4-addition reactions [1]. Our contribution to the chemistry of these synthetic scaffolds illustrates the structural diversity that can be achieved by exploring their chemical behavior, whose key feature is the strong electrophilic character. Nitroso- and azoalkenes, including 3-tetrazolyl- and 3-triazolyl derivatives, were used for the alkylation of five-membered heterocycles, namely pyrroles, dipyrromethanes, indoles and furans [2–11]. Furthermore, new routes to bis(heteroaromatic)methanes have been developed via two consecutive hetero-Diels–Alder reactions (or conjugated additions) of the in situ generated nitrosoalkenes and azoalkenes, namely the synthesis of dipyrromethanes [12,13], bis(indolyl)methanes [14–16], bis(pyrazol-1-yl)methanes [17] and tetrapyrrolic compounds [18]. The latter led to the development of a novel synthetic approach to *meso*-substituted corroles, comprising the synthesis of bilanes via the reaction of nitrosoalkenes with dipyrromethanes, followed by oxidative macrocyclization [18].

The chemistry of 3-(1*H*-tetrazol-5-yl)-nitrosoalkenes and 3-(1*H*-tetrazol-5-yl)-azoalkenes is particularly interesting, as these building blocks can be used as a synthetic tool to explore carboxylic acid/tetrazole bioisosterism. The acidity of N-H of 5-substituted 1*H*-tetrazoles is similar to that of carboxylic O–H at physiological pH, both exhibiting planar structures, tetrazoles being more lipophilic. The tetrazole moiety displays stronger metabolic stability and several cases are known where the replacement of a carboxylate by a tetrazole group led to enhanced biological activity and metabolic stability [19–21]. In this context, novel tryptophan analogues, where the carboxylic group was replaced by the bioisosteric tetrazolyl functionality, were obtained by exploring the reactivity of 3-tetrazolyl-nitrosoalkenes towards indoles, leading to indoles bearing open-chain oximes, followed by the oxime reduction. These tryptophan analogues were used in the synthesis of biologically relevant

β-carbolines containing a tetrazole group via Pictet–Spengler condensation with aldehydes and further oxidation [22].

The synthesis of 3-tetrazolyl-1,4,5,6-tetrahydropyridazines via hetero-Diels–Alder reaction of 3-tetrazolyl-1,2-diaza-1,3-butadienes has also been reported [4]. These functionalized 1,4,5,6-tetrahydropyridazine derivatives are molecules with relevance from the chemical as well as the biological point of view, as the 1,4,5,6-tetrahydropyridazine ring is a structural motif commonly encountered in a wide variety of biologically active compounds [23–26]. Our study has unveiled the unusual chemical behavior of these 1,2-diaza-1,3-dienes (e.g., **2**) characterized by the participation in cycloaddition reactions with both electron-rich and electron-deficient dienophiles, as illustrated in Scheme 1, allowing the synthesis of adducts and cycloadducts with wider molecular diversity [4].
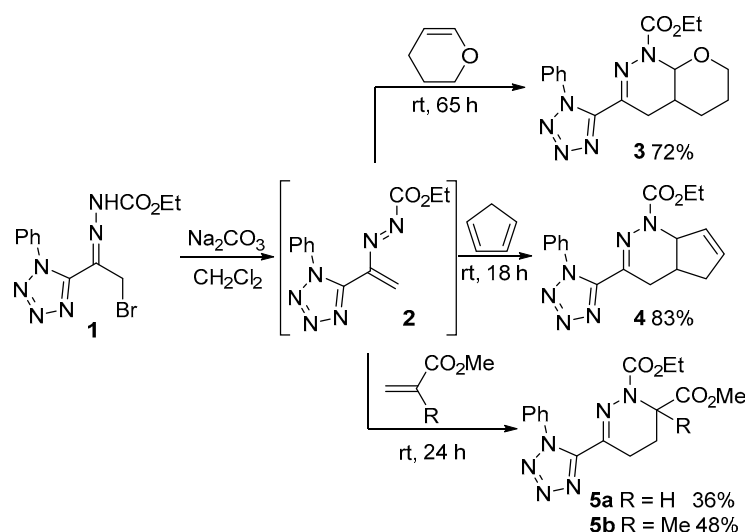


**Scheme 1.** Synthesis of 3-tetrazolyl-1,4,5,6-tetrahydropyridazines via hetero-Diels–Alder reaction of a 3-tetrazolyl-1,2-diaza-1,3-butadiene.

In this communication, further insights into the reactivity of 3-tetrazolyl-1,2-diaza-1,3-butadienes are disclosed.

## 2. Results and Discussion

The unusual reactivity pattern of 3-tetrazolyl-1,2-diaza-1,3-butadienes, characterized by the reaction with both electron-rich and electron-deficient dienophiles, led us to explore the Diels–Alder reaction of these hetero-dienes with methyl vinyl ketone (**6**). The transient diaza-1,3-butadiene **2** was slowly generated from hydrazone **1** [4] in dichloromethane, by the action of sodium carbonate, at room temperature in the presence of the dienophile. However, the expected cycloadduct was not formed and instead product **7** was isolated in 29% yield (Scheme 2).
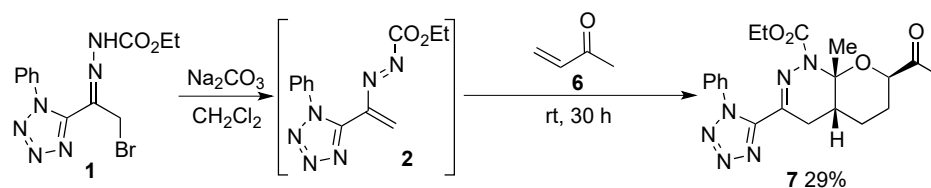


**Scheme 2.** Reaction of ethyl 3-(1-phenyl-1*H*-tetrazol-5-yl)-1,2-diaza-1,3-butadiene-1-carboxylate (**2**) with methyl vinyl ketone.

The structural assignment of this compound could only be achieved by X-ray analysis (Figure 1). The compound is comprised of two *cis* fused six-membered rings, a hexahydro-7*H*-pyrano[2,3-*c*]pyridazine ring system, with four substituents. There are three chirogenic

centres C-4a, C-7 and C-8a. Two molecules of opposite chirality are present in the crystal structure. However, only the enantiomer with (*R*,*R*,*R*) configuration is shown in Figure 1, for clarity. The tetrahydropyridazine ring has a half-chair conformation, whereas the tetrahydropyrano ring has a chair conformation. The methyl group at C-8a is in an axial position with respect to the tetrahydropyridazine ring, whereas the hydrogen H-4a is in a bissectional position with respect to the same ring. The acetyl group at C-7 is in an equatorial position.
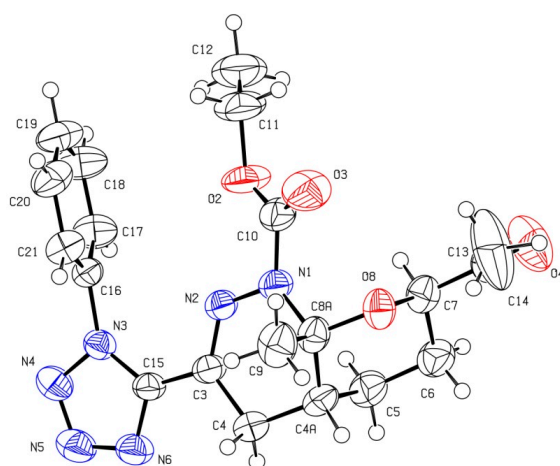


**Figure 1.** ORTEP-3 diagram of compound **7** with anisotropic displacement ellipsoids drawn at the 50% probability level. The methyl groups at C12 and C14 are disordered over two alternate positions; for clarity, only one of these positions is shown.

The synthesis of heterocycle **7** can be explained considering that the methyl vinyl ketone dimer **8** was present in the reaction medium and acted as a dienophile in the hetero-Diels–Alder reaction with diaza-1,3-butadiene **2**. In fact, we could confirm by $^1$H NMR that a 93:7 mixture of the methyl vinyl ketone (**6**) and 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**8**) was used instead of pure methyl vinyl ketone. To confirm these observations, compound **8** was prepared via the Diels–Alder reaction of methyl vinyl ketone, as described in the literature [27]. The reaction of hydrazone **1** with dimer **8** in the presence of sodium carbonate gave 3-(tetrazol-5-yl)-hexahydro-7*H*-pyrano[2,3-*c*]pyridazine **7** in very high yield as single regioisomer (Scheme 3).
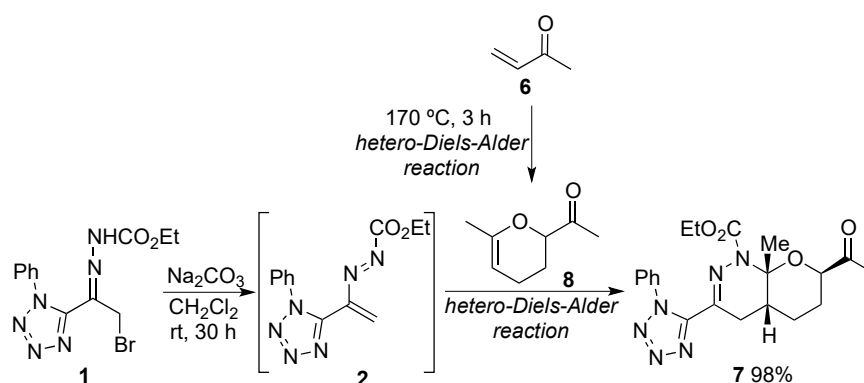


**Scheme 3.** Synthesis of ethyl 7-acetyl-8a-methyl-3-(1-phenyl-1*H*-tetrazol-5-yl)-1,4,4a,5,6,8a-hexahydro-7*H*-pyrano[2,3-*c*]pyridazine-1-carboxylate (**7**).

Frontier molecular orbitals (FMO) analysis was previously carried out for hetero-Diels–Alder reactions of diaza-1,3-butadiene **2** and ethyl vinyl ether, as an electron-rich dienophile model, and methyl acrylate, as an electron-deficient dienophile model [4]. This study demonstrated that the cycloaddition reaction was controlled by the LUMO$_{azoalkene}$-

HOMO$_{dienophile}$ interaction for both dienophiles. Furthermore, the calculated difference in energy of the relevant frontier orbital of diaza-1,3-butadiene **2** and ethyl vinyl ether was lower ($\Delta E = 3.13$ eV) than for the reaction with methyl acrylate ($\Delta E = 4.96$ eV), indicating that the studied azoalkene reacts preferentially with electron-rich dienophiles. This observation is in agreement with the results obtained for the above-described reaction, in which diaza-1,3-butadiene **2** only reacted with the electron-rich dienophile **8** when in the presence of a 93:7 mixture of methyl vinyl ketone and 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**8**).

## 3. Materials and Methods

### 3.1. General Information

The NMR spectra were recorded on a Bruker Avance III instrument operating at 400 MHz ($^1$H) or at 100 MHz ($^{13}$C). Chemical shifts are expressed in ppm relatively to internal tetramethylsilane (TMS). IR spectrum was recorded on a Nicolet 6700 Fourier Transform spectrometer. HRMS spectrum was recorded on a Finnigan MAT95 S electrospray (ESI) TOF mass spectrometer. Melting point was recorded on a Reichert hot stage. Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash chromatography was performed with silica gel 60 as the stationary phase. Ethyl 2-[2-bromo-1-(1-phenyl-1*H*-tetrazol-5-yl)ethylidene]hydrazine-1-carboxylate (**1**) [4], obtained as single isomer, and methyl vinyl ketone dimer (**8**) [27], were prepared as described in the literature.

### 3.2. Synthesis of Ethyl 7-Acetyl-8a-methyl-3-(1-phenyl-1H-tetrazol-5-yl)-1,4,4a,5,6,8a-hexahydro-7H-pyrano[2,3-c]pyridazine-1-carboxylate 7

To a solution of ethyl 2-(2-bromo-1-(1-phenyl-1*H*-tetrazol-5-yl)ethylidene)hydrazine-1-carboxylate (**1**) (0.140 g, 0.39 mmol) and methyl vinyl ketone dimer **8** (0.547 g, 10 equiv., 3.9 mmol) in CH$_2$Cl$_2$ (30 mL), Na$_2$CO$_3$ (0.210 g, 5 equiv., 1.98 mmol) was added and the reaction mixture stirred at room temperature for 30 h. The mixture was then filtered through a celite pad, which was washed with dichloromethane. The solvent was evaporated off and the product purified by flash chromatography [ethyl acetate/hexane (1:1)] to give compound **7** as a white solid (0.157 g, 98%). mp: 161.6–163.5 °C (from ethyl acetate/hexane). IR: (KBr) 692, 766, 1112, 1286, 1311, 1619, 1717, 1734, 2923, 2986 cm$^{-1}$. $^1$H NMR: (400 MHz, CDCl$_3$): δ = 1.09 (t, 3H, *J* = 7.2 Hz), 1.27–1.38 (m, 1H), 1.48–1.58 (m, 1H), 1.67 (s, 3H), 1.80–1.84 (m, 1H), 1.96–2.02 (m, 2H), 2.28 (s, 3H), 2.98–3.10 (m, 2H), 3.74 (dd, 1H, *J* = 11.6 and 2.0 Hz), 3.91–3.95 (m, 1H), 4.04–4.08 (m, 1H), 7.49–7.55 (m, 5H, Ar*H*). $^{13}$C NMR: (100 MHz, CDCl$_3$): δ = 14.4, 24.8, 26.0, 26.03, 26.3, 30.8, 34.8, 62.3, 76.3, 87.4, 126.0, 129.1, 129.9, 132.8, 135.3, 150.9, 152.3, 208.3. HRMS (ESI+): calcd for C$_{20}$H$_{25}$N$_6$O$_4$, 413.19318 [M+H]$^+$; found, 413.19323.

### 3.3. Crystallographic Data for Ethyl 7-Acetyl-8a-methyl-3-(1-phenyl-1H-tetrazol-5-yl)-1,4,4a,5,6,8a-hexahydro-7H-pyrano[2,3-c]pyridazine-1-carboxylate 7

C$_{20}$H$_{24}$N$_6$O$_4$, M = 412.45, *triclinic*, *P*-1 with unit cell, *a* = 9.6243(3) Å, *b* = 9.8590(2) Å, *c* = 12.5952(3) Å, α = 68.645(2)°, β = 72.467(2)°, γ = 75.230(2)°, *V* = 1047.06(5) Å$^3$. It contains two molecules/unit cell. $\rho_{calcd.}$ = 1.308 g/cm$^3$, Z = 2, μ = 0.094 mm$^{-1}$. *R* [*I* > 2σ(*I*)] = 0.0465 and $R_w$ = 0.1359 for 3684 independent reflections. H atoms were placed at calculated positions and refined as riding on their parent atoms. The methyl groups at C12 and C14 were found to be disordered over two alternate positions in the analyzed crystal.

## 4. Conclusions

The efficient Diels–Alder reaction of ethyl 3-(1-phenyl-1*H*-tetrazol-5-yl-1,2-diaza-1,3-butadiene-1-carboxylate with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (methyl vinyl ketone dimer) leading to the corresponding 3-(tetrazol-5-yl)-hexahydro-7*H*-pyrano[2,3-c]pyridazine derivative is reported. The structural assignment of this cycloadduct was achieved by X-ray analysis.

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